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Interview with Dr. Joshua Lederberg, August 26, 1994

TL: The Sabia virus that's been in the news..

JL: I think it's of Argentinean origin and there's been some concern about the transmission of arena-viruses from rodents to people, especially as new lands are opened up for agriculture and so on.

TL: These viruses aren't related to the Ebola and Marburg viruses, are they?

JL: I don't think so, but they illustrate the same point about evolution and pathogenesis, but they're not genetically related as far as I know.

TL: The New Yorker article a few years ago mentioned that a whole village died during an epidemic with the Ebola virus..

JL: Yes. Well what we don't know is how much was transmission from person to person, and how much from animal reservoirs. With as many people as were infected, there is a suspicion that person to person transmission played a role, but it's very hard to reconstruct that.

TL: But if it was person to person, then it makes it unlikely that it was that contagious, otherwise more people would have died, or?

JL: There's a lot we don't know, there are many pandemics that might have got started and didn't. In 1975 there was an outbreak of a virus that resembled swine flu. It was quite severe, entered only a small population and for reasons totally amazing to us, it smoldered and flickered out. It didn't spread very widely, and we have no idea why. It had all the earmarks that it was going to do that, and locally it did. There were some 60 or 80 soldiers who came down with it and several fatalities. That was something that was very scary and there was an effort at that time - not an effort, it was concluded - to develop a major vaccination program against this virus. It then turned out to be not so necessary, because for reasons we just don't know, it died out. Let's hope we're as lucky next time.

TL: There was a statement in the book that pathogens tend to become less virulent over time.

JL: That is a feeble general principle. It's probably true, but there are conflicting evolutionary trends. And we're operating here mostly on theory and a little bit on natural history and direct observation. The theoretical insight is that a virus that kills its host promptly, is less likely to spread to other individuals than one that leaves its host intact. The virus wants to maximize the number of virus particles and wants to have a host from which to proliferate for as long as possible. Those are

slightly incompatible objectives, because the more the virus grows, the more virulent it's likely to be. But the ideal virus from the point of view inevitably spreading everywhere is one that proliferates extensively, that is excreted by the host carrying it but never kills its host. Because then the live host is there to infect others over a very long period of time. And with an even greater point of subtlety, if it's not that dangerous, then we will not take the measures to prevent its further spread, than if it were the case if it were a highly virulent organism. So we have the view that that will be the natural evolution and if we look around in nature, we find that there are a lot of viruses in different species. We have all our childhood viruses, which under good circumstances are not terribly lethal.

TL: And they used to be?

JL: They can be, for example mumps is quite a severe disease in an adult, but if you get it as a child, it generally isn't. The same is true of polio and hepatitis virus, so there are many examples where the virus, when it's spread under what seems under more general primitive conditions is not so harmful, but when you have hosts that have not been inured to it, then it can become very dangerous. We also see viruses in many animals, where it's not particularly serious in those animals... The Hanta virus is probably an example that we don't know too much about the natural ecology of it, but we don't see evidence that it's as dangerous for the mice as it is for the people once it gets across the species barrier. So we have some confirmation of viruses that have lived together with their hosts for long periods of time have evolved into a more stable equilibrium. That's not much consolation in the short-run and there is a different short-run trend, namely that within a given infected host, the virus that multiplies the more rapidly is going to win out within that host. That may not be the best in the long-run from the point of view of propagation, but inside the host you get evolutionary pressure towards greater virulence. So there are a lot of contradictions, making it all the more difficult to predict what the long-term balance is going to be.

TL: I read an article saying that the Aids virus may becoming less virulent, for instance in the long-term survivors.

JL: Yes, there are pretty good hints about that and one would have expected that to have happened. Besides Aids, and some other viruses, but Aids outstandingly, is genetically very unstable. Because it depends not on DNA-replication but on RNA transcription, basically. That's much more error-prone. There's no editing mechanism in transcription and so almost every particle of Aids is different in at least one nucleotide. The mutation-rate is close to one per particle. So you are by chance just going to have a lot of less virulent mutants in any Aids-virus population. Now if those are less virulent, but still populate the host, then you'll have the evolution you've just described. It's a plausibility argument, we can't be absolutely certain that's how

it happened, and it's not yet definitively established that the long-term survivor is carrying a more latent strain. But it makes perfect sense. There's every reason to believe but there's no compelling proof yet.

TL: And vice-versa, the ones who die quicker may have a more virulent strain.

JL: They may have a more virulent strain or..these cases are always confounded by what is the physiological state of that particular host or the genetic state. There may be individuals who may be genetically predisposed to a different reaction to the HIV. We know that's true if you compare people and primates. Very different course of the disease. With HIV in chimpanzees I don't think gives rise to immune breakdown at all or if so only over a very very long period of time. So there's something in the genetic constitution of the chimpanzee that makes it react very differently than the human. Well it's very likely that there are humans who differ from one another.

TL: That actually leads to another question. Designing an Aids vaccine, the pharmaceutical will probably concentrate on the strains that are prevalent in the Western world..

JL: Well, they will change their prevalence and other strains will take over.

TL: So if you're talking about preventive measures, basically it's really a development problem. You have to consider everything that's going on in other parts of the world.

JL: That's what I've tried to stress in my own writings. We're not an island. It's certainly development, it's not the whole story. Even in the same developmental situation we can have vastly different social and cultural contexts. What's been happening in Thailand, one can say that there will be retributions falling on them. But the extraordinary laxity and the abuse of young children, the commercialization of prostitution, the corruption that goes along with that. Businessman from Europe and from Japan going on sex-holidays to Thailand and believing that somehow they're going to get away with it. The wrath of nature is on their heads. But Thailand is not the same as other developing countries in that regard. Of course it's a development issue, but there are other factors as well.

TL: One of the questions is also, who is going to pay for it?

JL: That's one of the reasons I've been stressing the fact that we're not an island. It couldn't be more true or more pertinent here. We better figure out how to pay for it, if only for self-interest, if you discard every altruistic and humanitarian motive, we will suffer the consequences individually and locally if we don't take a global perspective on the matter. And I'm hoping that will enhance the motivation to be concerned about the disease. The very minimum is setting up a global surveillance network, knowing

what's cropping up here and there. But that has to be coupled with health-care and prophylactic measures. The outstanding success in that arena was the smallpox vaccination program, which has done everybody an enormous benefit. Most of the work had to be done in the Third World, where there was still a continuing reservoir of infection, but it has relieved the entire world of a great burden and has saved an enormous amount of money, even just for the West. It's very hard to get this message across and I think in the current decade where we're seeing an isolationist trend in that .. let the world stew in its own juice.. the carelessness of what goes on. It's punctuated every now and then, when CNN will go in and show a famine and a massacre, and there'll be some half-hearted effort. Even those response have become blunted, and I think the next famine that CNN shows, we'll get no response. I'm just very discouraged at how few people will open their eyes and take a global perspective.

TL: The effort taken on the polio virus, is that focussed only on the Americas?

JL: Well it has, but there's a campaign to try to spread it elsewhere. And there will be the same arguments. We can never rest really easy, we can eradicate - we have essentially eradicated polio. There has been no indigenous case in the Western Hemisphere in the last 3 or 4 years. There have been some cases but they have all been imports. Those imports don't spread very far, because of continued vaccination. If we relent on vaccination they will come back again.

TL: And why isn't that taken up by the WHO?

JL: The WHO is merely an intergovernmental organization. It only does what governments are willing to invest in. WHO is not a perfect instrument. It is riven with politics at every level. You have to expect that it will be if it's at the mercy of governmental officials of every stripe and not all from responsible democratic regimes. We have to work with it, it's the best we got, and if we didn't have it, we'd have to reinvent it. You asked a very revealing question. It's existence may be very mischievous, if people think, well, there's somebody looking after it. That's only the beginning of the discussion. They are an intergovernmental establishment, they have grand headquarters with pomp. We had a meeting on Global Problems of Infectious Diseases and they're having troubles raising 75,000 dollars to publish the proceedings.

TL: You mentioned several times that the US should take the lead in this effort.

JL: It has to. We are still a great power. It has a very different meaning today than it did a few years ago. We have a lot of economic competition, though you may want to question that designation. We account for a very large part of the medical expertise and medical research capability, and as flawed as it is

from the international perspective. If I complain about what our attitudes are, if you look at most of Europe or most of the world, they are more isolationistic in their views and they're preoccupied with regional issues. A few countries have been counter-examples, the Swedes and the Canadians, have been very important and disproportionate contributions to global problems. But not much will happen without a US leadership. This administration has had domestic affairs very much on its mind, it's very hard to get much of a stir. Also in financing. It will have to be shared responsibilities, but again the US is going to have to show leadership. There need to be reforms in the agencies, the WHO, the UNESCO. Not everything has gone right in the political constructions of these organizations. And that's been one obstacle. When there are scandals it's hard to draw up activity and draw more interest to drop more money on the pond.

TL: Specifically, for instance in developing a vaccine. Industry is not going to do it on its own. So is it going to be governmental money?

JL: Absolutely.

JL: The National Research Council is the permanent staff, several hundred people that work in Washington on a numerable range of science policy studies, usually at the behest of a government agency or Congress. In a few cases they get private funding and do something on their own. The IOM report is an example of the latter.

TL: The response of the government?

JL On an intellectual level it's been very favorable. A lot of people have been mobilized not only to think about it, but to work in convergent way. It's become the spearhead for the CDC's effort as you've seen a copy. That's the government agency's response to this. But in general it's very hard to get money for anything these days. But nature has conspired with us, a lot of things have just happened in the last few years, that fit right in line with the dire concerns. Luckily they're ghastly enough to warrant some attention and yet haven't reached a point of major pandemic and wipe-out. We haven't had another Aids. The one we have is bad enough, but we have things like the Hanta-virus outbreak, hemorrhagic E. coli, they're all listed.

TL: What do you think are the major threats for the next decade or so?

JL: It depends what we do about it? If we were not reacting in some other ways, I would have said that the thing most certain looming over our head - immediately even more than tuberculosis - are the drug resistant coccal infections. WE could expect overnight news of a further infectious outbreak of vancomycin-resistant staphylococcus. This is just the nightmare, that people are sort of waiting for.

TL: Would that affect mainly older, bedridden patients?

JL: Lots of people. None of these things is really going to stay out in one place. If you really had a major source of vancomycin-resistant bugs, then it's bound to spread, not just in hospitals. Those are things we can do something about and there at least the beginnings of a reaction. Over a little bit longer of a time scale, because TB doesn't spread quite that rapidly, I'd put that on the list. And yet there's been a very energetic public health response to it - not as energetic in antibiotic development, but that's coming out as well. Until 2 years ago I would have said that over - it's likely it'll happen in a 10 or 20 year time-scale - that another flu like 1919 is something that has the rapid spread of universal infection. Nobody was not infected, it just spread so rapidly. With the lethality of the particular virus that we had in 1919, that killed between 0.5 and 1 percent of the population in Western Europe and the United States, probably more in other countries with less well developed health care. And we don't even know that that's the limit, but I like to stick to things for which there is a specific historic precedence. Well that's going to happen. The genetic mechanisms for those kinds of strains returning the example over time. Viruses are being churned out all the time and I don't believe we have a response mechanism in place, which is nearly up to the task of recognizing a threat, developing and distributing the vaccine for it. So we're really going to be in for it, unless we change the way we think about it. My view is that we need to find some kind of cassette, which would quickchange parts. We can do that with genetic engineering. So that we could develop it very very quickly when we see a new strain and not have to worry too much about safety aspects of it because we know about being able to separate the appropriate epitopes from the lethal factors, so that leads in non more than a few weeks to large scale production of the vaccine.

TL: You said that up to 2 years ago you would have predicted this..

JL: Well the Hanta virus really scares me. That's something that's just materialized in a very different way. We don't know why we're not seeing more of it. The virus is present in rodent populations all over North America. It's very behavior is very much like the flu, except it's major route of transmission is in another animal species. That could break out too, that's a very nasty disease. Once the symptoms start occurring, there's nothing we can do for it, It's had a very high attack rate. Those are the things we know about, we could be absolute certain that there are dozens of other comparable situations that just haven't broken to the surface.

TL: What about the changing structure of the population? Will the increasing proportion of the older people change anything?

JL: It does a little bit. But with flu young people were dying. It

seemed to be totally non-discriminating. Basically it got in so fast, there was no time for anybody to develop an immune response to it, young or old. So it really cut right across every age group. So that is certainly potentially a factor but... Paradoxically, older people may do better. That is because they've been around longer and they've had more chance to be immunized by a previous exposure, if only by cross-reacting antigens of various kinds. So you have to be old and decrepid to start going the other way, but certainly even our standard flu.. what I call our garden variety of flu.. probably only accounts for 5 to 10 percent of our deaths today. It's a number most people don't realize how much terminal illness ends up being influenza. It might not have happened if people weren't enfeebled by other illnesses, but it is reported on death certificates in close to 10 percent of cases. So that may play a role, but I don't want to exaggerate it. People who are immunocompromised for a variety of reasons, from HIV has been the outstanding example - they're so vulnerable to so many different infectious agents, and then in turn they provide a kind of seed-bed for the further fomenting and further evolution as we've seen in TB.

TL: SO if one of those very virulent influenza strains were to appear next year.. with the standing strategies that we have right now, they wouldn't be very effective, would they?

JL: I don't think so. It depends on how quickly in fact it does spread. Here we are worse off than in 1919 because we have people literally travelling all around the world, by the thousands and tens of thousands on a daily basis. Hundreds of thousands if you're talking just about intracontinental, so its speed of propagation would certainly be much faster than 1919.

TL: So we can be lucky that there aren't more lethal viruses.

JL: If there were more than we've had, then we wouldn't be here as a species. So far we've had an uneasy equilibrium with viruses. We haven't been wiped out. Every 50 years or so one comes along with a major threat, but with an order or a percent or a few percent of the population. From the point of view of global view of population, maybe there's not much to worry about, small flickers in the overall curve, and we can reproduce faster to compensate for it. But especially the amount of misery that that generates, it's definitely a major threat. One percent, that means somebody you know, in your circle of friends, means somebody could be dying this year from this flu.

TL: Talking about the strategies trying to contain diseases. An important factor I imagine is having laboratories to try to identify the agents.

JL: That's a key to it. If you don't know what's going on, there's not much you can do about it. So I think having a global network of laboratory capability, replicating what we have in Atlanta and does what it does all around the world and establishing

communications.. It's a social and political as well as a technical issue.

TL: If something is discovered in Kenya, is it sent over to the CDC?

JL: Sometimes it is and sometimes it isn't. Some governments are not too happy about disclosing that they have disease within their borders, they're afraid that it'll affect tourism. So it's not automatic, but that's why an informal network does not have to go through government channels to get permission to report certain circumstances. And one that doesn't excite a lot of press attention the minute something comes up.

TL: So that it would go directly from Kenya to some computer network?

JL. There would be a lab in Kenya, if there's any special reagents they need or something that's beyond their immediate skills, then it should be distributed to whatever other labs have the special skills. Something like it goes on now, but it's not coherent, it's not systematic.